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## Essential fatty acids and inflammation

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## Essential fatty acids and inflammation

Essential fatty acids are 'essential'<sup>1</sup> not only because of their physiological importance but because they must be derived in either direct or partially elaborated form from the diet. Thus these acids may be classified as vitamins (indeed they were once called vitamin F).

Two groups of fatty acids are essential to the body: the  $\omega 6$  (n6) series, derived from linoleic acid (18:2 n-6) and the  $\omega 3$  (n3) series, derived from  $\alpha$ -linolenic acid (18:3 n-3). In these notations 18 is the number of carbon atoms in the molecule, the second number is the number of double carbon-carbon bonds (degree of unsaturation), and the number after the n is the position of the first double bond starting from the methyl ( $\omega$ ) end of the fatty acid chain. The figure shows the sequences of the two fatty acids. Fatty acids provide energy, are an integral part of cell membranes, and are precursors for prostaglandins, thromboxanes, and leukotrienes, collectively termed eicosanoids. Abundant experimental evidence supports the view that eicosanoids participate in development and regulation of immunological and inflammatory responses. Because most rheumatic diseases are characterised by inflammation, disordered immune regulation, and tissue injury there is much interest among rheumatologists in the role of eicosanoids in regulation of host defences. As the detrimental effects of therapy for the rheumatic diseases may be more difficult to manage than the diseases themselves there is a need for new, safe approaches to the treatment of these patients. Alteration of the eicosanoid profile by administration of fatty acid precursors other than arachidonic acid is one approach under investigation.

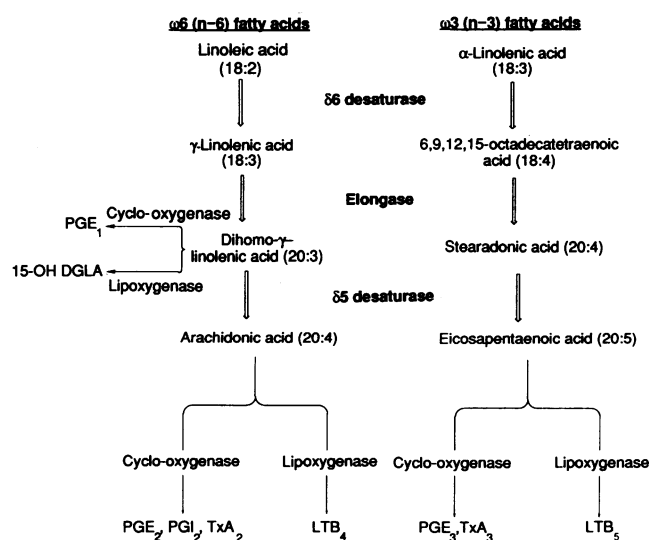
As eicosanoids derive from essential fatty acids, dietary manipulation or direct administration of precursor fatty acids has been used to alter the eicosanoid profile. Although changes in eicosanoid production owing to alteration of fatty acid intake form the basis of the current hypothesis for the anti-inflammatory effects of this type of treatment, it is likely that the precursor fatty acids themselves may alter immune responses. Animal and human studies have shown that changes in essential fatty acid intake alter the fatty acid composition of cell membranes.<sup>2</sup> For example, in essential fatty acid deficiency,

deprivation of linoleic acid leads to deficiency of arachidonic acid and impairment of prostaglandin synthesis. Essential fatty acid deficiency causes many pathological changes, but it also reduces the severity of inflammation in experimental animal models. Fasting also has a salutary effect on symptoms of patients with rheumatoid arthritis.<sup>3</sup> As neither induction of essential fatty acid deficiency nor fasting are likely to be popular treatments it might be more prudent to modify or supplement, rather than delete, lipid intake.

The extraordinary rapidity with which platelets adhere to damaged tissue, aggregate, and release potent biologically active materials suggests that the platelet is well suited to be a cellular trigger for the inflammatory process.<sup>4</sup> Thus efforts directed at suppression of thromboxane synthesis, enhancement of prostacyclin (prostaglandin  $I_2$ ) production, and inhibition of platelet aggregation may result in limitation of inflammatory responses. Fish oil lipids, rich in eicosapentaenoic acid (20:5 n3), inhibit formation of cyclo-oxygenase products (thromboxane  $A_2$ , prostaglandin  $E_2$ ) derived from arachidonate. Newly formed thromboxane  $A_3$  has much less ability than thromboxane  $A_2$  to constrict vessels and aggregate platelets. In addition, production of prostaglandin  $I_2$  by endothelial cells is not reduced appreciably by increased eicosapentaenoic acid content, and the physiological activity of newly synthesised prostaglandin  $I_3$  is added to that of prostaglandin  $I_2$ .<sup>5</sup> Diets enriched in fish oil also reduce the amount of leukotriene  $B_4$  generated via the 5-lipoxygenase pathway in stimulated neutrophils and monocytes, suppress the chemotactic response of neutrophils to leukotriene  $B_4$ , and reduce generation of platelet activating factor, interleukin 1, and tumour necrosis factor by stimulated monocytes.<sup>6-7</sup> Fish oil supplements have therefore been used in attempts to suppress inflammation in experimental models and in patients with rheumatoid arthritis.<sup>8-10</sup> Therapeutic benefits have been modest but encouraging. Evidence that fish oil administration enhances collagen induced arthritis in rats and exacerbates vasculitis in autoimmune mice<sup>11</sup> dictates caution in the premature uncontrolled use of fish oil treatments in inflammatory diseases.

Evidence obtained from experiments in vitro and in vivo in small animals and humans suggests that other novel fatty acids may be safe and effective anti-inflammatory and immunomodulatory agents. For example, certain botanical lipids, notably those extracted from seeds of the evening primrose and borage plants, contain relatively large amounts of  $\gamma$ -linolenic acid (18:3 n-6). This acid is converted rapidly to dihomogamma-linolenic acid (20:3 n-6) the fatty acid precursor of the monoenic prostaglandins—for example, prostaglandin  $E_1$ . In humans the  $\delta 5$  desaturase which converts dihomogamma-linolenic acid to arachidonic acid is sluggish. Thus concentrations of arachidonate do not increase appreciably. Dihomogamma-linolenic acid competes with arachidonate for oxidative enzymes, thereby reducing production of cyclo-oxygenase products derived from arachidonate. In addition, dihomogamma-linolenic acid cannot be converted to inflammatory leukotrienes by 5-lipoxygenase. Instead, it is converted to 15-hydroxydihomogamma-linolenic acid, which has the added ability of inhibiting 5-lipoxygenase activity.<sup>12</sup>

$\gamma$ -Linolenic acid enrichment of diet suppresses acute and chronic inflammation as well as joint tissue injury in several experimental animal models.<sup>13</sup> In animals treated with evening primrose or borage seed oils, cells from inflamma-



Metabolic pathways of essential fatty acids.  $PGE_n$ =prostaglandin  $E_n$ ; 15-OH DGLA=15-hydroxy-dihomo- $\gamma$ -linolenic acid;  $TxA_n$ =thromboxane  $A_n$ ;  $LTB_n$ =leukotriene  $B_n$ .

tory exudate are enriched in  $\gamma$ -linolenic acid and its elongated product dihomogamma-linolenic acid. Exudate prostaglandin  $E_2$  and leukotriene  $B_4$  concentrations are reduced and leucocyte effector functions (chemotaxis, lysosomal enzyme release) are suppressed. Enrichment with dihomogamma-linolenic acid of synovial cells in culture leads to a marked reduction of prostaglandin  $E_2$  synthesis, a substantial increase in prostaglandin  $E_1$  production, and reduction in interleukin 1 induced synovial cell proliferation. Addition to cultures of arachidonic acid (which increases prostaglandin  $E_2$  substantially) or eicosapentaenoic acid does not modify synovial cell proliferation. The antiproliferative effect of dihomogamma-linolenic acid is prevented by indomethacin.<sup>14</sup> Thus both marine and botanical lipids have anti-inflammatory actions owing to their ability to reduce synthesis of oxygenation products of arachidonic acid which are potent mediators of inflammation.

In addition to their role as eicosanoid precursors, fatty acids are of major importance in maintaining cell membrane structure and are key determinants of the behaviour of membrane bound enzymes and receptors.<sup>15</sup> The fatty acid precursors can exert these functions directly and therefore may themselves be important regulators of immune responses. Dihomogamma-linolenic acid suppresses interleukin 2 production by human peripheral blood mononuclear cells in vitro, suppresses proliferation of interleukin 2 dependent human T lymphocytes, and reduces expression of activation markers on T lymphocytes directly, in a manner which is independent of conversion to prostaglandin.<sup>16</sup> The observations indicate that fatty acids can modulate immune responses by acting directly on T cells and suggest that alteration of cellular fatty acids may be a worthwhile approach to control of inflammation.

Inflammation is central to the cutaneous manifestations of psoriasis and atopic eczema. In both conditions leukotriene  $B_4$  and 12-hydroxyeicosatetraenoic acid concentrations are increased in affected skin. Controlled trials, in which  $\gamma$ -linolenic acid (in primrose seed oil) was used to treat atopic eczema, showed sufficient clinical benefit to warrant approval of such treatment by the National Health Service.<sup>17</sup>

Administration of 1.1 g/day  $\gamma$ -linolenic acid to volunteers and patients with rheumatoid arthritis for 12 weeks (in an uncontrolled manner) resulted in enrichment of leucocytes with dihomogamma-linolenic acid, significant reductions in monocyte prostaglandin  $E_2$  and leukotrienes  $B_4$  and  $C_4$ , and reduced synovitis in six of seven patients.<sup>18</sup> Other studies have shown that  $\gamma$ -linolenic acid administration leads to increased prostaglandin  $E_1$  production by monocytes.<sup>19</sup> A preliminary report<sup>20</sup> indicating that 1.2 g  $\gamma$ -linolenic acid/day given to normal volunteers for six weeks reduced interleukin 1 production by stimulated peripheral blood monocytes may also be relevant to its potential therapeutic effects.  $\gamma$ -Linolenic acid (540 mg/day in primrose seed oil) has been shown, in a 12 month long placebo controlled, double blind study to reduce pain and the need for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis.<sup>21</sup> Lower doses of the acid (480 mg/day), used for shorter periods of time (12 weeks), were not useful treatment for patients with rheumatoid arthritis.<sup>22, 23</sup> It may be of interest that in one of the negative studies<sup>22</sup> the  $\gamma$ -linolenic acid supplement could be substituted for the non-steroidal anti-inflammatory drugs. Clearly, long term, multicentre, placebo controlled studies of a large number of patients are needed to determine whether any form of treatment is useful for patients with rheumatoid arthritis.

Few adverse effects of marine or botanical lipid administration have been noted; stool softening and abdominal bloating have been reported. Nonetheless, potential adverse effects cannot be dismissed. Experience teaches that the longer a given treatment is used the greater the incidence of

adverse effects. Administration of long chain polyunsaturated fatty acids increases the likelihood of lipid peroxidation with its associated toxic effects on cells. It is not known whether an increased requirement for an antioxidant (such as vitamins E and C) accompanies increased intake of long chain unsaturated fatty acids. Because these novel fatty acids can reduce inflammation and affect immunocytes the question arises as to whether they can compromise the immune system. Susceptibility to infection has not been seen as yet but must be considered.

The potential ability of particular fatty acids to regulate cell activation, immune responses, and inflammation is exciting to consider at the clinical, cellular, and molecular levels. A better understanding of how fatty acids modulate function of cells involved in host defence might lead to development of new, benign treatment for diseases characterised by acute and chronic inflammation.

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